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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/441,966	11/17/1999	RODERICK L. HALL	98.736-A	5234

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/441,966	HALL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 15-22* is/are pending in the application.

4a) Of the above claim(s) *18,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,15,19 and 22* is/are rejected.

7)☒ Claim(s) *16 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

[2] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/6/2005 has been entered.

[3] Claims 1-10 and 15-22 are pending in the application.

[4] Applicants' amendment to the claims, filed 6/6/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[5] Applicants' amendment to the specification, filed 6/6/2005, is acknowledged.

[6] Applicants' arguments filed on 6/6/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[8] Claims 18 and 20-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

[9] Claims 1-10, 15-17, 19, and 22 are being examined on the merits only to the extent the claims read on the elected subject matter.

Claim for Domestic Priority

[10] Applicants' claim for domestic priority under 35 U.S.C. § 120 to non-provisional application 09/218,913, filed 12/22/1998, is acknowledged.

Claim Objection(s)

[11] Claims 1, 15, and 19 are objected to in the use of an improper sequence identifier. It is suggested that applicants use the proper sequence identifier "SEQ ID NO:" in the claims. See 37 CFR 1.821(d).

[12] Claims 1 and 19 are objected to as reciting non-elected subject matter. It is suggested that applicants remove non-elected subject matter from the claims.

[13] Claims 16-17 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

[14] Claim 22 is objected to as the claim does not end with a period. See MPEP 608.01(m).

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[15] Claims 2-10, 15, 19, and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention. This is a new matter rejection.

Claim 22 (claim(s) 2-10, 15, and 19 dependent therefrom) recites the limitation "wherein the rate of mucocillary clearance is increased by more than about 30 percent, compared with the rate of mucocillary clearance in the absence of the treatment." MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description". Applicants rely on pp. 80-81 and Figures 22 and 26 as showing support for the recited

limitation of claim 22. However, the recited claim limitation goes beyond the subject matter originally filed.

Figure 22 shows increased TMV in *sheep* (not any subject as encompassed by the claim) using *3mL of a 3mg/mL* solution of the peptide (not any "effective amount" as encompassed by the claim) increases TMV *at eight hours* (not any time period as encompassed by the claim) as compared to control. It is also noted that applicants take great liberty in arriving at a TMV that is "about 30%," using values of about 98% TMV with peptide and about 76% TMV without peptide. Further, even assuming *arguendo* one recognized that the values of about 98% TMV with peptide and about 76% TMV without peptide, it is noted that the claim recites "increased by more than about 30 per cent," which encompasses any value of TMV – up to 100%.

Similarly with Figure 26, the figure shows increased TMV in a *guinea pig* (not any subject as encompassed by the claim) using *10 micrograms* of the peptide (not any "effective amount" as encompassed by the claim) *at 2.5 hours* (not any time period as encompassed by the claim) increases TMV as compared to control. Again, applicants take great liberty in arriving at a TMV that is "increased by more than about 30 per cent" and, as noted above, "more than about 30 per cent" as recited in the claim encompasses any value – up to 100%.

It is suggested that applicants "show support" for the claim in accordance with 35 U.S.C. 112, first paragraph, and MPEP § 2163.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[16] Claims 1-10, 15, 19, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamburini et al. (WO 97/33996; cited in the Office action mailed 10/3/2003) in view of Rasche et al. (*Arzneim Forsch* 25:110-116; cited in the Office action mailed 10/3/2003) and O'Riordan et al. (*Am J Respir Crit Care Med* 155:1522-1528; cited as reference 17 in the IDS filed February 10, 2000). The claims are drawn to a method for accelerating the rate of mucociliary clearance in a subject by administering to the subject a serine protease inhibitor comprising SEQ ID NO:8 and a physiologically acceptable carrier.

Tamburini et al. teaches a human Kunitz-type serine protease inhibitor and a fragment thereof that has an amino acid sequence (page 7) that is 100% identical to SEQ ID NO:8 of the instant application. Tamburini et al. teaches human placental bikunin and fragments thereof, including SEQ ID NO:8, are contemplated as therapeutics for fibrotic disorders including pulmonary fibrosis (page 22, lines 21-23) and further teaches their peptides are contemplated for use in the medical/therapeutic applications suggested for native aprotinin (TRYSALOL®) or aprotinin analogues including diseases for which use of the human protein is indicated by virtue of its ability to inhibit human serine proteases such as inhibition of neutrophil elastase for treatment

of pulmonary emphysema (page 22, lines 32-34 and page 23, line 13). Tamburini et al. teaches various methods of delivery of human placental bikunin for therapeutic use (pages 24-27). Tamburini et al. teaches various advantages of using human placental bikunin in place of aprotinin (TRYSALOL ®) such as being of human origin, thus reducing risk of immunological reaction and being less positively charged than aprotinin thereby reducing the risk of kidney damage (page 24, lines 10-16). Tamburini et al. teaches those cysteine residues where such disulfide bonds are likely to occur (page 34, bottom, page 35, top). Tamburini et al. does not teach administration of their human placental bikunin specifically for increasing the rate of mucociliary clearance in a subject.

Rasche et al. teach a study of inhalation administration of aprotinin (TRYSALOL®) and the effects on patients suffering from chronic obstructive bronchitis including patients suffering from emphasematous pulmonary changes (page 110). Rasche et al. teach two effects of aprotinin (TRYSALOL®) administration were improved expectoration by the patient and a liquification of the sputum (page 116, left column).

O'Riordan et al. generally teach antigen-induced bronchial constriction is associated with mucociliary clearance and discusses the associated role of neutrophil elastase. Specifically, O'Riordan et al. teach an inhibitor of neutrophil elastase is able to increase mucociliary clearance as measured by tracheal mucus velocity (TMV) (see, e.g., Figure 2) and suggest that elastase inhibitors may be useful in the treatment of mucociliary dysfunction in asthma (page 15427, right column, bottom).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Tamburini et al., Rasche et al., and O'Riordan et al. for a method of accelerating the rate of mucociliary clearance by administering the human placental bikunin of SEQ ID NO:8 as taught by Tamburini et al. One would have been motivated to administer SEQ ID NO:8 to a subject in order to accelerate the rate of mucociliary clearance because Tamburini et al. taught that SEQ ID NO:8 can be used as a neutrophil elastase inhibitor in place of aprotinin for treatment of pulmonary emphysema in combination with the teachings of Rasche et al. who taught aprotinin administration in patients suffering from chronic obstructive bronchitis including patients suffering from emphasematous pulmonary changes had improved expectoration by the patient and a liquification of the sputum and the teachings of O'Riordan et al. who taught inhibition of neutrophil elastase results in increased mucociliary clearance and suggests that elastase inhibitors may be useful in the treatment of mucociliary dysfunction in asthma. One would have a reasonable expectation of success for a method of accelerating the rate of mucociliary clearance by administering the human placental bikunin or fragments thereof comprising SEQ ID NO:8 because of the results of Tamburini et al., Rasche et al., and O'Riordan et al. Therefore, claims 1-10, 15, 19, and 22 drawn to a method of increasing the rate of mucociliary clearance as described above would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO ARGUMENT: Applicants respond to the instant rejection at pp. 13-16 of the response filed 6/6/2005. Applicants argue the claimed invention "contains

Examples 11-26 which is not disclosed in Tamburini." While applicants acknowledge that Tamburini et al. disclose the sequence of SEQ ID NO:8, Tamburini et al. does not teach the use of SEQ ID NO:8 for increasing mucociliary clearance. Applicants argue that because Tamburini et al. disclose that "human placental bikunin is much more effective than bovine derived aprotinin as a serine protease inhibitor" and because Tamburini et al. fails to disclose working examples that show that human placental bikunin is effective for increasing mucociliary clearance, Tamburini et al. alone does not make the claimed invention obvious. Applicants argue that Tamburini et al. does not teach treatment of a patient to increase mucociliary clearance and therefore, is not a proper prior art reference.

Applicants' argument is not found persuasive. In response to applicant's arguments against the reference of Tamburini et al., one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The prosecution history is clear in that the rejection is based on the *combination* of Tamburini et al., Rasche et al., and O'Riordan et al.

Addressing the combination of the references of Tamburini et al. and Rasche et al., applicants argue that a *prima facie* case of obviousness is not met because Rasche et al., which teaches the therapeutic use of aprotinin, cannot be used in combination with Tamburini et al. because Tamburini et al. teaches away from using aprotinin by disclosing that their human bikunin has improved activity over aprotinin.

Applicants' argument is not found persuasive. The examiner agrees with applicants' statement that Tamburini et al. teaches away from using aprotinin to the extent that Tamburini et al. teach substituting aprotinin with human bikunin for advantageous reasons, including human bikunin being of human origin, thus reducing risk of immunological reaction, being less positively charged than aprotinin thereby reducing the risk of kidney damage, and, as acknowledged by applicants, being more effective than aprotinin. These teachings are noted above. In view of the teachings of Tamburini et al., there are expected clear advantages to administering human bikunin in place of aprotinin for treatment of chronic obstructive bronchitis as taught by Rasche et al. According to MPEP 2144, the expectation of some advantage is the strongest rationale for combining references.

Applicants argue that Rasche et al. is silent with regard to mucociliary clearance, and, according applicants, combining Rasche et al. with Tamburini et al. is not suggested as the combination does not teach all limitations.

Applicants' argument is not found persuasive. Again, it is noted that the rejection is based on the combination of Tamburini et al., Rasche et al., and O'Riordan et al. However, assuming *arguendo* the rejection did not rely on the teachings of O'Riordan et al., it is noted that replacing aprotinin with human bikunin for treatment of chronic obstructive bronchitis, as taught by the combination of Tamburini et al. and Rasche et al., would have inherently resulted in an increase in the rate of mucociliary clearance.

Addressing the combination of the references of Tamburini et al. and O'Riordan et al., applicants acknowledge that Tamburini et al. teaches human bikunin inhibits

neutrophil elastase, applicants argue Tamburini et al. teaches away from using aprotinin because human bikunin has improved inhibitory functions over aprotinin.

Applicants' argument is not found persuasive. Again, it is noted that the rejection is based on the combination of Tamburini et al., Rasche et al., and O'Riordan et al. The examiner agrees with applicants' statement that Tamburini et al. teaches away from using aprotinin to the extent that Tamburini et al. teach substituting aprotinin with human bikunin for advantageous reasons, including human bikunin being of human origin, thus reducing risk of immunological reaction, being less positively charged than aprotinin thereby reducing the risk of kidney damage, and, as acknowledged by applicants, being more effective than aprotinin. These teachings are noted above. In view of the teachings of Tamburini et al., there are expected clear advantages to administering human bikunin in place of aprotinin for increasing mucociliary clearance as taught by O'Riordan et al. According to MPEP 2144, the expectation of some advantage is the strongest rationale for combining references.

Conclusion

[17] Status of the claims:

Claims 1-10 and 15-22 are pending.

Claims 18 and 20-21 are withdrawn from consideration.

Claims 16-17 are objected to as improperly multiply dependent.

Claims 1-10, 15, 19, and 22 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656